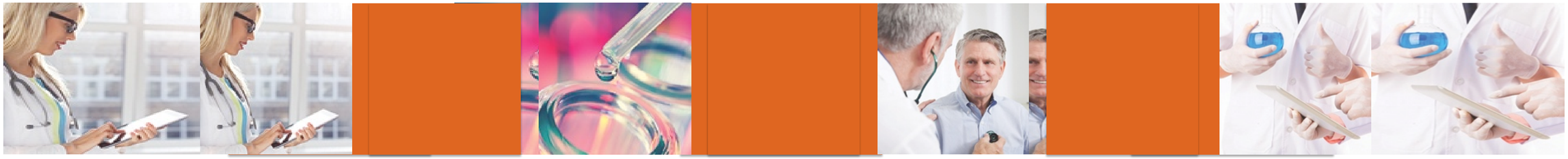
European Federation of Pharmaceutical Industries and Associations

EMA/EC multi-stakeholder workshop to further improve the implementation of the paediatric regulation
20 March 2018



Topic 4
Improving the handling of PIP applications

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Session 4 “Improving the handling of PIP applications”:

The main objective of this session is to identify operational challenges in relation to paediatric procedures and exchange ideas for process improvements.
We would like to invite you to present the industry’s point of view regarding the following two questions:

Which procedural and operational challenges in relation to paediatric processes as described in the PIP guideline (PIP, modification, waiver, compliance check) should be addressed?
What are constructive solutions that could facilitate efficient and robust operational framework (e.g. submission requirements, timelines, outputs and technical/administrative aspects)?

This should be a **10-minute statement** (maybe more) supported by **up to ~5 Powerpoint slides**.

How things have changed in 10 years...

- **In the 10 years since the first implementation of the Regulation, there has been...**
  - Changes in the regulatory environment: new legislation (update of the Financial Penalties Regulation, new Pharmacovigilance legislation), launch of the EudraCT public website and posting of results
  - Changes in the way EMA works, such as the introduction of PRIME, and the increasing voice of the experts and patients in procedures
  - Changes within industry itself, with specialised paediatric staff or department created for paediatric development support in most companies
  - Changes to the environment, with the arrival of new technical solutions and scientific advances, e.g. molecular targeted therapies
- **It is important that the improvements to the PIP application process take these into account, and that the learnings from other areas of EMA are brought to the development of medicines in children**

Improving the handling of PIP applications
3 priority areas to address

Scientific content

Detailed PIPs are agreed very early and need to be modified repeatedly

- The details agreed at the end of Phase I are based on assumptions and on the standard of care and competitive environment at the time
- Resources are spent on products that will not reach any further stages of development (attrition)
- Burden on industry and regulators as PIPs are agreed that will never progress, or will need to be repeatedly modified

- **Addressing this challenge will help design better studies that will allow the generation of data on the use in children in a better way**

PIP process

PIP procedures do not allow enough dialogue before and during the process

- The possibility for a dialogue before filing a PIP are limited
- Once a procedure starts, there is little to no opportunity for discussion with PDCO and no possibility of involving other stakeholders
- Many PIP applications and PIP modifications are withdrawn as agreement cannot be reached, or time pressure on companies can result in agreed PIPs that are difficult/impossible to complete
- Paediatric development is global, and there should opportunity to align with other regions

- **Addressing this challenge will help to have PIPs procedures that run better, and with more predictable outcomes**

Documentation

The documents and related procedures are complex

- Assembling applications is a burdensome process, as it is not possible to re-use information already submitted
- Some areas of uncertainty still remain
- Obligations are extremely detailed and alignment on compliance is unduly complicated

- **Adressing this challenge will help to have clearer documents, and reduce the burden**

Scientific content
Detailed PIPs are agreed too early and have to be modified repeatedly

- Solution:
  Acknowledge that a PIP needs to be built progressively, with staggered binding commitments that fit more naturally within the drug overall development process, with iterations that are informed by the availability of data and the input of other stakeholders

Acknowledge that a PIP needs to be built progressively (1)

- We continue to file PIP early, as per the Regulation, bur use sequential submissions to build an **‘iterative PIP’**:
  - The first PIP contains
    - All the measures that can already be agreed at this point in time, based on the existing data,
    - As well as a timeline of the development milestones (e.g. results from pre-clinical or adult studies) that are necessary to inform the further proposed iteration(s) of the PIP.
      - The key binding elements will include this timeline, ensuring that the PIP is submitted again to the PDCO at the next appropriate development milestone
      - The timeline can also include a natural point at which alignment across regions can be sought if applicable (e.g. end of Phase II)
  - The next iteration of the PIP will include
    - Modifications of agreed elements an/or new elements based on newly available data,
    - And further milestone dates at which the PIP will be re-submitted to PDCO
  - This can be repeated until all necessary measures are agreed

Acknowledge that a PIP needs to be built progressively (2)

- This solution is inspired by the PRIME scheme, where companies are asked to come back at given times for further regulatory input
- This is particularly suitable in certain situations e.g. PIPs where extrapolation is used, as it allows for a natural adjustment of the extrapolation plan as new data emerge
- Aligning the time of agreement on the clinical studies with the product development timelines ensures that studies are more likely to start shortly after the agreement has been obtained and therefore may not need to be deferred
  - In particular deferrals requested to wait for the result of adult studies should become unnecessary

PIP process
PIP procedures do not allow enough dialogue before and during the process

- Solution:
  Learn from the best practices within other EMA processes, in particular those for marketing authorisation applications and variations to revisit the procedures for agreeing on a PIP or on a PIP modification to bring in more dialogue.
  Use Scientific Advice and Orphan Designation procedures as best practice examples to explore what can enable cross-regional alignment

Bring to the PIP procedures the learnings from other EMA procedures (1)

- An increased scientific dialogue before MA filing makes for a better dossier
  - → use this model for PIP procedures
    - Improve the ‘early paediatric interaction’, consider involving other committees (CHMP/SAWP, COMP, CAT, as appropriate) and other stakeholders including patients and carers
    - Ensure that the input from Scientific Advice is accepted by PDCO

- Ensure that the PIP procedures allow sufficient opportunities for questions, responses and discussions
  - All MA procedures allow sufficient rounds of questions, stop clocks to prepare responses and opportunities for discussion (teleconferences, oral explanations) to ensure that agreement can be reached (multiple lists of outstanding issues at Day 180 for initial MA, multiple RSIs for extension of indication)
    - → use this model for PIP procedures
      - PIP initial procedure: in addition to the list of questions at day 60, include the possibilty for one or more list(s) of outstanding issues at day 90
      - Request for modification (RfM) procedure: include the possibility for at least one list of questions at day 60
        - Also allow the possibility of raising questions before the procedure via a pre-submission meeting

Bring to the PIP procedures the learnings from other EMA procedures (2)

- Consider a simplified RfM procedure to speed up timelines for specific simple changes (e.g. alignment of PIP prior to compliance check)
- Bring learnings from the Scientific Advice (SA) and Orphan Designation (OD) procedures on ensuring better regional alignment (e.g. application forms, joint procedures, templates)

Documentation
The documents and related procedures are complex

- Solution:
  Seek to simplify wherever possible by re-assessing which data or information is actually needed and why. Re-visit the key binding elements in the view of the experience of the past 10 years to identify what is truly critical to the objectives of the PIP.
  Consider looking at existing guidance to see where it can improved.

Seek to simplify wherever possible

- Evaluate how the documentation that is submitted can be simplified or improved
  - Further simplify the key binding elements and ensure that only critical information is listed
  - Evaluate whether all the data or information that are collected are necessary
    - Consider the use of cross-reference to documents already submitted in other procedures e.g. Investigators brochure, OD, SA, MA dossier
    - Consider the concept of a CTD-like approach that aligns the documentation for all regions and could allow for a regional module for EU-specific information
- Look into areas with the most queries and consider where guidance needs updating or creating (scope of the PIP, single/multiple PIP, etc.)
- Simplify compliance check to a single check on PIP completion
  - Re-evaluate the basis for partial compliance checks, and assess if they can be made optional
  - Re-evaluate the process for the final compliance check and seek for simplication
    - Self-certification by applicants that is formally checked at validation
    - Clarification on when it is appropriate for the PDCO to be involved

Conclusions

Learning from the past 10 years, we believe that:

- The creation, agreement on and conduct of a PIP that fits more naturally within the drug development process will improve the scientific credibility of the PIP and reduce the need for long deferrals for study starting dates
- It can offer greater certainty to all that the agreed PIPs can be effectively completed, and lead to more new medicines for children.
- Earlier and better scientific dialogue can facilitate this, along with the involvement of an extended expert base for evaluating proposed paediatric development, with the inclusion of the patient and carer perspective.

We look forward to working with EMA and other stakeholders on these improvements.